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Review

Zyxin and paxillin proteins: focal adhesion plaque LIM domain proteins go nuclear

Yuan Wang, Thomas D. Gilmore *

Department of Biology, Boston University, 5 Cummington Street, Boston, MA 02215-2406, USA

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Abstract

Zyxin and paxillin are the prototypes of two related subfamilies of LIM domain proteins that are localized primarily at focal adhesion plaques. However, recent work has shown that zyxin/paxillin family proteins also shuttle through the nucleus. These proteins may enter the nucleus by association with other proteins, but are exported from the nucleus by means of intrinsic leucine-rich nuclear export sequences. Zyxin/paxillin proteins may regulate gene transcription by interaction with transcription factors. In some cases, misregulation of nuclear functions of zyxin/paxillin proteins appear to be associated with pathogenic effects.

Keywords: Zyxin; Paxillin; Focal adhesion; LIM domain; Nuclear-cytoplasmic shuttling; Transcription

1. Introduction

Focal adhesion plaques are structures that form at the ends of actin fibers and serve as sites for force transmission. The integrins, a family of transmembrane proteins, are the primary proteins at focal adhesion plaques and function to connect the extracellular matrix to actin filaments, although this connection also requires many actin-attachment proteins and other cytoplasmic adhesion proteins. Thus, proteins at focal adhesion plaques form multiple interactions and signal transduction networks, which regulate cell adhesion, spreading, and motility, but which also convey signals into the nucleus to regulate gene transcription, cell proliferation, differentiation and apoptosis. Major signaling molecules that transmit information from focal adhesion plaques include FAK, Src family kinases, MAPK, and Rho family members, among others, which signal to the nucleus by a cascade of enzymatic reactions [1].

In the last few years, several related LIM domain proteins have also been implicated in the regulation of cytoskeletal dynamics and signal transduction at focal adhesion plaques. LIM domains are cysteine-rich motifs that are present in a large number of proteins and they appear to be involved primarily in protein–protein interactions. The group of LIM domain proteins at focal adhesion plaques includes zyxin, paxillin, and several related proteins. These proteins do not have enzymatic domains, and their functions are likely to depend on their roles as adaptor proteins for the assembly of multiple protein complexes in different subcellular compartments.

The regulation of actin dynamics, cell movement, and signal transduction by zyxin/paxillin proteins is mediated by their association with a variety of cytoskeletal and signaling proteins (see Table 1) (reviewed in Refs. [2,3]). This review will focus on emerging evidence that these

Abbreviations: AP-1, activator protein-1; BPV, bovine papilloma virus; CAKβ, cell adhesion kinase β; FAK, focal adhesion kinase; HMG, high-mobility-group; HPV, human papilloma virus; ILK, integrin-linked kinase; JAB1, Jun activation domain-binding protein 1; LD repeats, leucine–aspartate repeats; LIM domain, Lin-11 Isl-1 Mec-3 domain; LPP, lipoma preferred partner; MAPK, mitogen-activated protein kinase; MLL, mixed lineage leukemia; NES, nuclear export signal; NLS, nuclear localization sequence; PAK, p21-activated kinase; PKL, paxillin kinase linker; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; PYK2, proline-rich tyrosine kinase 2; SH3, Src homology domain 3; Trip6, thyroid hormone receptor interacting protein 6; TTF1, thyroid transcription factor 1; VASP, vasodilator-stimulated phosphoprotein

* Corresponding author. Tel.: +1-617-353-5444, +1-617-353-5445; fax: +1-617-353-6340.

E-mail address: gilmore@bu.edu (T.D. Gilmore).

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Table 1
Interaction partners of zyxin/paxillin family proteins

Protein	Cytoskeletal and/or plasma membrane[a]	Signaling molecules[a]	Transcription factors/ nuclear proteins	Others[a]
Zyxin	α-actinin Mena/VASP CRP H-warts/LATS1	Vav CasL p130^{Cas}	HPV E6 protein [22] SON DNA-binding protein [32]	
Trip6	OpaP Tropomyosin 4	Grb2 PTP-BL/1E CasL p130^{Cas} Synaptic GTPase activating protein	Thyroid hormone receptor [15] Retinoid X receptor [15] v-Rel [17] gp210 [32] SON DNA-binding protein [32] Atrophin-1 related protein [32]	RIL Novel protein
LPP	Mena/VASP			
Ajuba		Grb2 GLT1	TTF1 [19]	
Paxillin	β1, β3, α4 and α6 integrin subunits Syndesmos Tubulin Vinculin Actopaxin Schwannomin	FAK CAKβ/Pyk2 ILK Src PKL PAK Csk Crk PTP-PEST	BPV E6 protein [33,34]	Poly(A)-binding protein 1
Hic-5	Vinculin Syndesmos Actopaxin Dopamine transporter	FAK CAKβ/Pyk2 PKL Csk PTP-PEST GLT1	Androgen receptor [18] Glucocorticoid receptor [5]	
Leupaxin		CAKβ/Pyk2		

[a] For a full reference list for the interacting proteins in this table, go to http://www.nf-kb.org (under Gilmore Lab Publications).

LIM domain proteins also have functions in the nucleus.

2. Structure and general features of zyxin and paxillin family proteins

Zyxin/paxillin proteins have two major domains, an N-terminal half that contains proline-rich sequences (some of which are SH3 domain binding sites) and a C-terminal LIM domain region (Fig. 1). The zyxin subfamily includes zyxin, Trip6 (thyroid hormone interacting protein 6), LPP (lipoma preferred partner), and Ajuba [2]. All zyxin family proteins have three LIM domains towards their C termini. These proteins share high sequence similarity, especially within the LIM domain region.

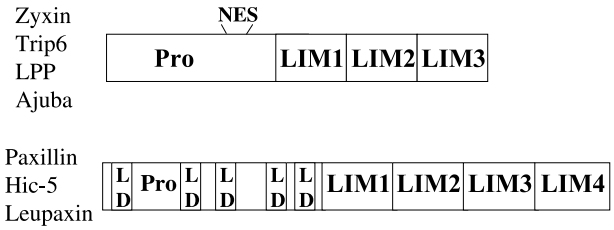

Fig. 1. Generalized structures of zyxin and paxillin family proteins. Pro, proline-rich sequences; LD, LD repeats; NES, nuclear export signal; LIM, LIM domains. See text for more details. Two other proteins, Testin [35] and LIMD1 [36], have three C-terminal LIM domains related to the zyxin family, but they do not have N-terminal proline-rich regions and thus are not included here.

Mammalian paxillin family members include paxillin, Hic-5 and leupaxin [3]. As distinguished from the zyxin subfamily, paxillin family proteins have additional protein interaction domains within the N-terminal domain, i.e., multiple LD repeats, and they have four C-terminal LIM domains. Although paxillin family members share extensive similarity within their LIM domains and LD repeats, other regions within their N-terminal domains are quite divergent.

3. Zyxin/paxillin proteins shuttle between focal adhesion plaques and the nucleus

In most cell types, zyxin/paxillin proteins are detected primarily in focal adhesion plaques at steady state. However, in some cases, these proteins have also been detected in the cytosol or the nucleus. For example, a small fraction of zyxin and Hic-5 can be detected in the nucleus of rat

embryo fibroblasts [4,5], and Ajuba is primarily a cytosolic protein in mouse 3T3 cells [6].

Two lines of evidence have recently indicated that zyxin/paxillin proteins shuttle between cytoplasmic and nuclear compartments. First, treatment of cells with leptomycin B, an inhibitor of Crm1-dependent nuclear export, causes zyxin/paxillin family proteins to accumulate in the nucleus [6–11]. Second, a leucine-rich nuclear export signal (NES) has been identified within the N-terminal region of most zyxin/paxillin proteins, and mutation or deletion of this NES also results in their nuclear accumulation [4,6–10].

Although their NESs are well-characterized, less is known about how zyxin/paxillin proteins are imported into the nucleus. None of the zyxin/paxillin proteins has an obvious traditional (basic) nuclear localization sequence (NLS). Thus, these proteins either have unconventional NLSs or nuclear import mechanisms, or they enter the nucleus in association with other NLS-containing proteins. Zyxin and Trip6 have multiple sequences that have nuclear targeting functions, including sequences from both the N-terminal domain and the C-terminal LIM domain [9,10], and in the case of Trip6, these sequences can target a heterologous protein to the nucleus [10]. Similarly, N terminally truncated forms of Ajuba, paxillin, and Hic-5, containing essentially only the LIM domains, localize to the nucleus [5,6,12,13]. That zyxin/paxillin proteins can enter the nucleus by association with other proteins is reinforced by the finding that a mutant form of cell adhesion kinase β/proline-rich tyrosine kinase 2 (CAKβ/PYK2) that abnormally localizes to the nucleus also drags Hic-5 and paxillin to the nucleus [14] (see also discussion of E6, below).

4. Effects of zyxin and paxillin family proteins on transcription

LIM domains have structures related to certain zinc fingers, which are known to mediate DNA binding in several transcription factors. However, zyxin/paxillin proteins are probably not direct transcription factors, as only the LIM domains of Hic-5 have been shown to have DNA-binding activity, and this has only been demonstrated in vitro [7]. Nonetheless, several lines of evidence indicate that zyxin and paxillin family proteins act in the nucleus to affect transcription. First, zyxin/paxillin proteins interact with a variety of nuclear proteins (Table 1), including several transcription factors. Second, several zyxin/paxillin proteins (zyxin, Trip6, LPP, Hic-5) have transactivation ability when measured in reporter gene assays, usually as GAL4 fusion proteins [5,8,10,15,16]. In most cases, the majority of the transactivation activity is located within the N-terminal domain, but the LIM domain regions also have a weak ability to activate transcription. As zyxin/paxillin proteins essentially consist of multiple protein–protein interaction domains, the ability of these GAL4 fusion proteins to activate transcription must be interpreted with some caution, in that it is possible that GAL4 fusion proteins containing zyxin/paxillin proteins only serve to bring interacting transcription factors and their activation domains to the reporter loci, and thus do not reflect an intrinsic activity of the zyxin/paxillin proteins.

Nevertheless, the bulk of evidence indicates that zyxin/paxillin proteins regulate gene transcription as co-activators through interaction with transcription factors or the basal transcription machinery. Specifically, Trip6, Ajuba, and Hic-5 have been shown to affect the activity of specific transcription factors. For example, Trip6 was identified as a protein that interacts with thyroid hormone receptor and retinoid X receptor in a ligand-dependent manner [15], and Trip6 can enhance the transactivation ability of the retroviral oncoprotein v-Rel [17]. Similarly, the LIM domains of Hic-5 interact with the androgen receptor [18] and the glucocorticoid receptor [5]. Moreover, overexpression of Hic-5 can enhance the transactivation activity of several steroid receptors, including the glucocorticoid receptor, androgen receptor, estrogen receptor, mineralocorticoid receptor, progesterone receptor, and thyroid hormone receptor [5,18]; however, the ability of Hic-5 to enhance transactivation by the estrogen and thyroid hormone receptors also requires the co-activator GRIP1 [5]. In each of the above cases, a simple model is that the LIM domains of the zyxin/paxillin protein mediate the interaction with the transcription factor and the N-terminal domains act to enhance transcription; alternatively, the multiple interaction domains of the zyxin/paxillin proteins serve as nucleation sites for the recruitment of multiple co-activators for these specific transcription factors.

5. Biological consequences of nuclear activities of zyxin/paxillin proteins

Less is known about what biological functions zyxin/paxillin proteins regulate by acting in the nucleus and how or whether nuclear transport of zyxin/paxillin proteins is regulated. The most tantalizing evidence suggests that these proteins can affect steroid hormone receptor activity. As noted above (see also Table 1), Hic-5 and Trip6 interact with several steroid hormone receptors, in some cases, in a hormone-dependent manner [5,15,18]. Furthermore, treatment of embryonal carcinoma cells with retinoic acid causes relocalization of Ajuba from the cytoplasm to the nucleus, which coincides with the differentiation of these cells into an endodermal phenotype [6]. Moreover, overexpression of the LIM domain region of Ajuba, which accumulates in the nucleus of these cells, induces endodermal differentiation [6]. Finally, Ajuba interacts with the TTF-1 transcription factor, which is required for thyroid development [19]; however, it is not known whether Ajuba affects the activity of TTF-1.

In insects, naturally occurring nuclear forms of paxillin-related proteins appear to be involved in the control of muscle differentiation. That is, N terminally truncated forms of a homolog of a paxillin-like protein, which arise by alternative splicing, have been identified in muscle cells of

Table 2
Summary of nuclear activities of zyxin/paxillin family proteins

Protein	Nuclear-cytoplasmic shuttling	Transcriptional activation	Co-activator activity	DNA binding
Zyxin	+ [4,9]	+ [10,22]	?	?
Trip6	+ [10]	+ [10,15,16]	+ [17]	− [10]
LPP	+ [8]	+ [8]	?	?
Ajuba	+ [6]	?	?	?
Paxillin	+ [11]	?	?	?
Hic-5	+ [7]	+ [5]	+ [5,18]	+ [7]
Leupaxin	?	?	?	?

+, the protein has the indicated activity; −, the protein does not appear to have the indicated activity; and ? indicates that it has not yet been determined.

moths and *Drosophila*, in which they appear to be involved in controlling an aspect of developmentally programmed muscle cell death [20,21]. These short proteins consist of only three LIM domains, and at least in *Drosophila* cells can be detected in the nucleus [21]. It is not yet known whether there are alternative forms of zyxin/paxillin proteins in vertebrates that have alternative subcellular localization due to the lack of sequences that retain the protein at focal adhesion plaques or affect nuclear import or export.

In two situations, nuclear zyxin family sequences have been associated with human diseases. First, Dengenhardt and Silverstein [22] have recently shown that zyxin, via its LIM domain region, interacts with the E6 oncoprotein of human papillomavirus type 6, which is commonly associated with genital warts. Moreover, the interaction with E6 causes zyxin to move from focal adhesion plaques to the nucleus and enhances transcriptional activation by a GAL4-zyxin protein. Second, the human *LPP* gene, situated at chromosomal position 3q27-q28, is located at the junction of some disease-related chromosomal translocations, which result in the expression of chimeric LPP proteins. Specifically, C-terminal sequences of LPP become fused either to N-terminal sequences of the high-mobility-group protein HMGIC protein due to t(3:12) chromosomal translocations in benign human lipomas and pulmonary chondroid hamartomas [23–25], or to sequences of the mixed lineage leukemia (MLL) gene product in some secondary acute leukemias due to t(3:11) translocations [26]. In these cases, the chimeric proteins contain HMGIC or MLL DNA-binding domains fused to LIM domains of LPP. Moreover, the HMGIC-LPP fusion protein is located in the nucleus [8]. Given the common involvement of chimeric transcription factors in human cancer [27], the LPP LIM domains may contribute a transactivation domain or transcription factor interaction domain to the DNA-binding sequences of HMGIC and MLL to create novel and growth-promoting transcription factors. In fairness, however, it should be noted that these translocations also result in the expression of the reciprocal cDNAs containing the N-terminal proline-rich transactivation domains of LPP fused to C-terminal sequences (e.g., of HMGIC, MLL, or other proteins) in most of the above-described tumors (see Ref. [28]). Therefore, at this time, it is not known which, if any, of the LPP fusion proteins in a given tumor contributes to the growth of that tumor.

6. Concluding remarks

Accumulating evidence suggests that zyxin/paxillin proteins have nuclear functions that affect transcription (Table 2), in addition to their functions at focal adhesion plaques.

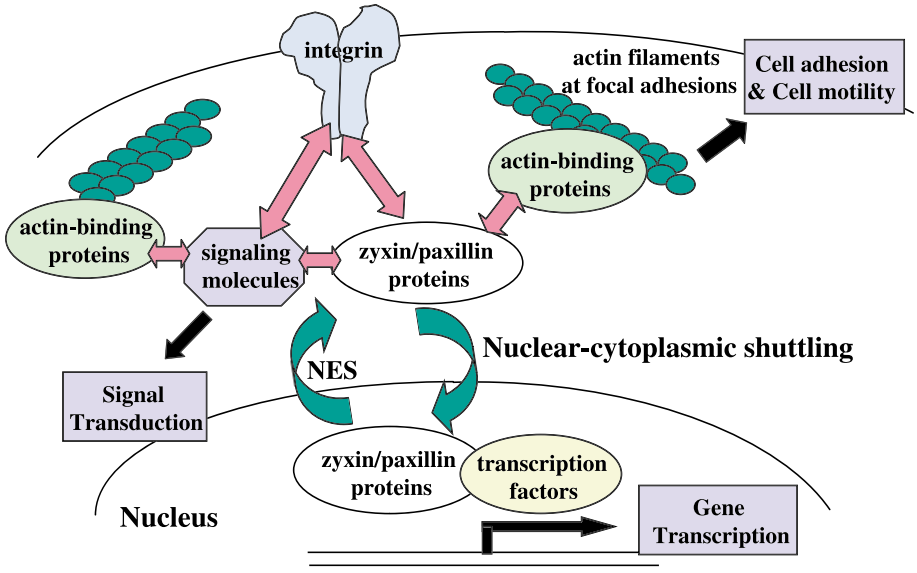

Fig. 2. Multiple functions of zyxin/paxillin proteins. At steady state, zyxin/paxillin proteins are located at focal adhesion plaques, where they interact with various integrin, actin binding, and signaling molecules (see text and Table 1) to affect cell adhesion, motility, and signal transduction. In addition, zyxin/paxillin proteins shuttle between cytoplasmic and nuclear compartments; the mechanism of nuclear import is not known, but nuclear export is mediated via an intrinsic NES in these proteins. In the nucleus, zyxin/paxillin proteins are likely to interact with transcription factors to enhance gene expression.

Indeed, zyxin/paxillin proteins may constitute a direct signaling pathway from cytoskeletal-plasma membrane networks to the nucleus (Fig. 2), much as has been proposed for the Wnt/β-catenin pathway [29], the AP-1 co-activator JAB1 [30] and the guanylate kinase CASK [31]. Alternatively, zyxin/paxillin proteins form platforms for the assembly of protein complexes, both at focal adhesion plaques and in the nucleus. It still remains to be determined what types of physiological processes may regulate the nuclear-cytoplasmic shuttling of zyxin/paxillin proteins, what genes or nuclear processes these proteins may affect, and whether misregulation of this signaling pathway is also involved in some diseases. The use of knockout cell lines or specific RNAi disruptions combined with cDNA microarray data may shed light on nuclear targets and activities of zyxin/paxillin proteins. In any event, the study of nuclear activities of zyxin/paxillin proteins will surely encompass an intriguing area for future study, as we unravel the complexity and dynamics of intracellular communication.

Acknowledgements

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